REMARKS

Applicant submits that the claims as amended are fully supported by the originally filed patent application and no new matter has been added. Applicants respectfully request entry and consideration of this amendment.

If the Examiner would like to discuss any of the issues raised in the Preliminary Amendment, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: 7/22/02

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REMARKS

Claims 1-59 are pending in the application. The Examiner has restricted the claims under 35 U.S.C. § 121 into five groups as follows:

I. Claims 1-24 and 33-42, drawn to peptides, classified in class 530, subclass 300;

II. Claims 25-27 and 31-32, drawn to DNA, classified in class 536, subclass 23.7;

III. Claims 28-30, drawn to antibodies, classified in class 530, subclass 387.1;

IV. Claims 43-51, drawn to methods of treating immune-mediated disease, classified in class 424, subclass 184.1; and

V. Claims 52-59, drawn to methods of modulating an immune response, classified in class 514, subclass 2.

In complying with the requirements of 37 C.F.R. § 1.143, Applicant hereby provisionally elects, with traverse, claims of Group I, representing claims 1-24 and 33-42, directed to peptides. In the event the Examiner withdraws the present restriction requirement in favor of a grouping as delineated below, Applicant elects for prosecution claims 1-24, 33-42, 43-51, and 52-59. Applicant traverses the present form of the restriction for the following reasons.

The Examiner has raised MPEP 803.04 for the proposition that because the claims refer to individual sequences, each comprise a separate invention, ostensibly requiring a separate application. Applicant respectfully traverses this notion. With respect to the independence and distinctness of inventions, the general principles laid out in the MPEP 806 state that where inventions are independent (*i.e.*, no disclosed relation therebetween), restriction is ordinarily proper. However, where inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Further, as clearly set forth in MPEP 806.03, where claims of an application define the same essential characteristics of a single disclosed embodiment of an invention, restriction should never be required. "This is because the claims are but different definitions of the same disclosed subject matter, varying in breadth or scope of definition." (MPEP 806.03)

The instant invention fits this very situation which can easily be recognized by the fact that all of the peptides are linked by the same single disclosed and claimed core embodiment, *i.e.* they are HLA pan DR-binding peptides as claimed in parent claim 1. Under the Examiner's cursory evaluation directed only to the physical embodiment of the sequences, this fundamental claimed element is improperly ignored.

Further, MPEP 803.04 is directed to nucleotide sequences, not peptide sequences. Even if peptide sequences are being treated in similar fashion, section 803.04 explicitly states that PTO policy is to waive the requirements of 37 C.F.R. 1.141 and permit a reasonable number of sequences, namely ten or less independent and distinct sequences with less than a ten sequence limit being reserved for highly complex situations. In the instant case, the peptide sequences are simple and comprise only 15 amino acids. Additionally, as is well documented in the MPEP (section 803.02), with respect to restriction of Markush-type claims where the members of the Markush group are sufficiently few in number and so closely related that a search and examination of the entire claim can be made without *serious* burden, the Examiner *must* examine all the members of the Markush group. Applicants respectfully bring to the Examiner's attention that the claims as amended include reference to peptides in the form of Markush groups in which there are only 9 peptide sequences. Further, as shown in the specification, particularly Table I, these sequences are somewhat conserved and are derived from only two sources, human and mycobacterium. Further still, they are also derived from a single family of protein labeled Hsp60.

Section 806.04 of the MPEP further defines independence of inventions such that, for example, two different combinations, "not disclosed as capable of use together," . . . are independent. The example refers to a shoe vs a locomotive bearing. In the instant invention, all of the elements (*i.e.*, molecules that can be used in immune modulation or therapy) are disclosed as capable of use together and are not unrelated as indicated by the spirit of the MPEP's example. Rather, they are related in the context of their immunologic utility as disclosed in detail in the specification and as claimed.

MPEP section 808.01 provides yet further clarification as to what is "independent." Specifically, "where [the inventions] are not connected in design, operation, or effect under the disclosure of the particular application under consideration (MPEP 806.04), the facts relied on for this conclusion are in essence the reasons for insisting upon restriction." In the instant case the various peptides are without question "connected in design, operation, [and] effect," in that they all fall under a single family of protein, have been shown to operate in a similar fashion in that they are HLA pan DR-binding peptides, and provide for the same physiological consequence (i.e., bring about immune stimulus) and otherwise are used in the operation of interactions with T cells to bring about the effect of modulating T cells. As a practical matter the peptides are "connected" to their method of use for therapys for treating/preventing the general category of immune-mediated disease by providing for modulating an immune response in a subject patient.

Therefore, Applicant traverses the Examiner's requirement that Applicant be restricted to a single sequence. Further, per the above argument, the kind of hsp (*i.e.*, its source) is irrelevant to a reason to require restriction. The Examiner has not provided any required showing that there is material distinction between hsps from different sources with respect to their HLA pan DR-binding characteristic.

Regarding the restriction of the claims of Group I from the claims of Groups IV and V, Applicant respectfully points out that MPEP 806.05(h) provides that distinction between a product and process of using can be shown (A) if the process of using *as claimed* can be practiced with another *materially* different product, or (B) the product *as claimed* can be used in a *materially* different process. Applicants submit that neither of these circumstances can be shown. The claimed methods of treating a subject (claim 43) and the claimed method of modulating an immune response (claim 52) require as elements administrating to a subject a peptide that is a stress protein fragment that binds to MHC class II molecules. The peptides of Group I are just such peptides. The methods with their consequent results specifically requires use of such stress peptides, not another product materially different or otherwise. The Examiner has provided no proof whatever as required for proving a prima facie case for there being a materially different product that can be used in the process as claimed to modulating an immune

response using stress protein fragment as in claims 52 and 43. Therefore, the method of use claims must be retained where there is no material distinction between the product and process of use.

The Examiner further proposes that distinction between the methods of Groups IV and V may be found in a difference in the selection of a patient with different symptoms. Applicants respectfully traverse this proposition as the condition of a particular patient is not relevant to the claimed methods. It is clearly a basic nature of medicine that each and every patient observed by a physician will exhibit variable symptoms. The claimed methods (claims 43 and 52) simply recite the treatment or prevention of an *immune-mediated disease* or modulation of *immune response* by administration of a particular composition. The individual nature of a treated subject is utterly irrelevant to the claim and consequently the search. As between the Grouped claims IV and V, the dependent claims referencing immune-mediated diseases and cancers would necessarily be located in the same search as dependent claims 47 and 49 of Group IV and claims 56 and 58 of Group V include the same elements.

Rather than the grouping of the claims as proposed by the Examiner, Applicant suggests that the claims of Group I and those of Groups IV and V be considered for prosecution in this application and that the claims of Groups II and III be restricted. If the Examiner requires Applicant to elect a particular peptide and/or disease/cancer simply for search purposes, so that the elected element can be searched against the prior art for determining allowability of the generic parent claims 1, 43, and 52, and the consequent search of the remaining members of the Markush groups of the Seq. Ids, disease and immune response, then Applicants provisionally elect Seq. Id. 5 (peptide listed in table I as p-4 human 242-256), rheumatoid arthritis, and melanoma.

No fee is believe due respecting the instant response, however, if any fee not covered is due, please charge our deposit account Number 50-1355 in the appropriate amount. If the Examiner needs to reach Applicants' representative, the direct telephone number is (858) 677-1456.

Respectfully submitted,

Date: July 22, 2002

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Exhibit A

Version with marking to show changes.

Please revise the claims as follows:

5. (Amended) The substantially pure peptide of claim 1, wherein the peptide is at least 70% identical to a sequence [as set forth in] selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 [or] and 10.

6. (Amended) The substantially pure peptide of claim 5, wherein the peptide is at least 80% identical to a sequence [as set forth in] selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 [or] and 10.

7. (Amended) The substantially pure peptide of claim 5, wherein the peptide is at least 90% identical to a sequence [as set forth in] selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 [or] and 10.

8. (Amended) The substantially pure peptide of claim 5, wherein the peptide is at least 95% identical to a sequence [as set forth in] selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 [or] and 10.

9. (Amended) The substantially pure peptide of claim 5, wherein the peptide has a sequence [as set forth in] selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 [or] and 10.

21. (Amended) The substantially pure peptide of claim 5, wherein one or more amino acid of the peptides selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 [or] and 10 has been substituted by one or more amino acid having a similar size, charge and or polarity.

34. (Amended) The immunomodulating composition of claim 33, wherein the fragment binds to at least one molecule selected from the group consisting of HLADR1, DR4, and DR7.

38. (Amended) The composition of claim 34, wherein the substantially pure peptide has a sequence [as set forth in] selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 [or] and 10.

43. (Amended) A method for treating or preventing an immune-mediated disease in a subject having or at risk of having the disease comprising administering to the subject, an effective amount of a substantially pure peptide comprising a fragment of a stress protein that [to] binds to MHC class II molecules in a pharmaceutically acceptable carrier, wherein the peptide modulates an immune response, thereby treating or preventing the disease.

51. (Amended) The method of claim 34, wherein the substantially pure peptide has a sequence [as set forth in] selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 [or] and 10.

53. (Amended) The method of claim 52, wherein the fragment binds to at least one molecule selected from the group consisting of HLADR1, DR4, and DR7.

59. (Amended) The method of claim 52, wherein the substantially pure peptide has a sequence [as set forth in] selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 [or] and 10.

Exhibit B

Copy of Claims as they stand after entry of this Amendment

1. A substantially pure HLA pan DR-binding peptide comprising a fragment of a stress protein that binds to one or more MHC class II molecules.

2. The substantially pure peptide of claim 1, wherein the peptide binds to HLADR1, DR4, and DR7.

3. The substantially pure peptide of claim 1, wherein the peptide comprises an amino acid sequence that is conserved between human and bacterial heat shock proteins.

4. The substantially pure peptide of claim 1, wherein the peptide comprises an amino acid sequence that is conserved between human and mycobacterial proteins.

5. The substantially pure peptide of claim 1, wherein the peptide is at least 70% identical to a sequence selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

6. The substantially pure peptide of claim 5, wherein the peptide is at least 80% identical to a sequence selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

7. The substantially pure peptide of claim 5, wherein the peptide is at least 90% identical to a sequence selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

8. The substantially pure peptide of claim 5, wherein the peptide is at least 95% identical to a sequence selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

9. The substantially pure peptide of claim 5, wherein the peptide has a sequence selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

10. The substantially pure peptide of claim 1, wherein the stress protein is a heat shock protein.

11. The substantially pure peptide of claim 10, wherein the heat shock protein is a bacterial heat shock protein.

12. The substantially pure peptide of claim 10, wherein the heat shock protein is a mycobacterium species heat shock protein.

13. The substantially pure peptide of claim 12, wherein the mycobacterium species heat shock protein is hsp65 or hsp60.

14. The substantially pure peptide of claim 10, wherein the heat shock protein is a mammalian heat shock protein.

15. The substantially pure peptide of claim 14, wherein the mammalian heat shock protein is a human heat shock protein.

16. The substantially pure peptide of claim 15, wherein the human heat shock protein is human hsp60.

17. The substantially pure peptide of claim 1, wherein the fragment is about 10 to 30 amino acids in length.

18. The substantially pure peptide of claim 17, wherein the fragment is about 15 to 25 amino acids in length.

19. The substantially pure peptide of claim 17, wherein the fragment is about 15 to 20 amino acids in length.

20. The substantially pure peptide of claim 1, wherein the peptide has one or more D- amino acids.

21. The substantially pure peptide of claim 5, wherein one or more amino acid of the peptides selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 and 10 has been substituted by one or more amino acid having a similar size, charge and/or polarity.

22. The substantially pure peptide of claim 1, wherein the peptide is covalently linked to an adjuvant.

23. The substantially pure peptide of claim 22, wherein the adjuvant is keyhole limpet hemocyanin, bovine serum albumin, human serum albumin or isologous IgG.

24. A pharmaceutical composition, comprising a peptide of claim 1 in a pharmaceutically acceptable carrier.

33. An immunomodulating composition for use in treating or preventing an inflammatory disorder comprising a substantially pure peptide comprising a fragment of a stress protein that binds to one or more MHC class II molecules in a pharmaceutically acceptable carrier.

34. The immunomodulating composition of claim 33, wherein the fragment binds to at least one molecule selected from the group consisting of HLADR1, DR4, and DR7.

35. The composition of claim 34, wherein the inflammatory disorder is an immune-mediated disease.

36. The composition of claim 34, wherein the immune-mediated disease is an auto-immune disease.

37. The composition of claim 34, wherein the immune-mediated disease is selected from the group consisting of multiple sclerosis (MS), rheumatoid arthritis, lupus erythrematosis, type I diabetes, scleroderma, myastenia gravis and ulcerative colitis.

38. The composition of claim 34, wherein the substantially pure peptide has a sequence selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

39. The composition of claim 34, further comprising a biological response modifier.

40. The composition of claim 39, wherein the biological response modifier is selected from the group consisting of a cytokine, a chemokine, a hormone, a steroid and an interleukin.

41. The composition of claim 40, wherein the biological response modifier is an interferon.

42. The composition of claim 39, wherein the biological response modifier is selected from the group consisting of IL-l(α or β), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, GM-CSF, M-CSF, G-CSF, LIF, LT, TGF-β, γ-IFN, TNF-α, BCGF, CD2, or ICAM.

43. A method for treating or preventing an immune-mediated disease in a subject having or at risk of having the disease comprising administering to the subject, an effective amount of a substantially pure peptide comprising a fragment of a stress protein that binds to MHC class II molecules in a pharmaceutically acceptable carrier, wherein the peptide modulates an immune response, thereby treating or preventing the disease.

44. The method of claim 43, wherein the subject is a mammal.

45. The method of claim 44, wherein the mammal is a human.

46. The method of claim 43, wherein the immune-mediated disease is an auto-immune disease.

47. The method of claim 43, wherein the immune-mediated disease is selected from the group consisting of multiple sclerosis (MS), rheumatoid arthritis, lupus erythrematosis, type I diabetes, scleroderma, myastenia gravis and ulcerative colitis.

48. The method of claim 43, wherein the immune-mediated disease is a cancer.

49. The method of claim 43 wherein the cancer is selected from the group consisting of melanoma, leukemia, lymphoma, lung, liver, kidney, brain, bladder solid tumors, retinoblastoma, sarcoma and connective tissue cancers.

50. The method of claim 43, wherein the immune-mediated disease is an infectious disease.

51. The method of claim 34, wherein the substantially pure peptide has a sequence selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 and 10.

52. The method for modulating an immune response in a subject comprising administering to the subject, an effective amount of a substantially pure HLA pan DR-binding peptide comprising a fragment of a stress protein that binds to one or more MHC class II molecules.

53. The method of claim 52, wherein the fragment binds to at least one molecule selected from the group consisting of HLADR1, DR4, and DR7.

54. The method of claim 52, wherein the subject is a mammal.

55. The method of claim 54, wherein the mammal is a human.

56. The method of claim 52, wherein the immune response is associated with an immune-mediated disease is selected from the group consisting of multiple sclerosis (MS), rheumatoid arthritis, lupus erythrematosis, type I diabetes, scleroderma, myastenia gravis and ulcerative colitis.

57. The method of claim 52, wherein the immune response is associated with an infectious disease.

58. The method of claim 52, wherein the immune response is associated with an immune-mediated cancer selected from the group consisting of melanoma, leukemia, lymphoma, lung, liver, kidney, brain, and bladder solid tumors, retinoblastoma, sarcoma, and connective tissue cancers.

59. The method of claim 52, wherein the substantially pure peptide has a sequence selected from the group consisting of SEQ ID Nos: 2, 3, 4, 5, 6, 7, 8, 9 and 10.